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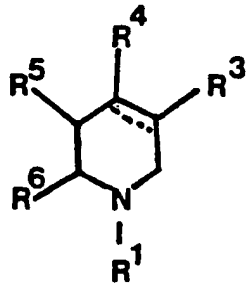
(54) Piperidine compounds and their preparation and use.

(57) New piperidine compounds having the formula



wherein

at least one of R^3, R^4, and R^5 are

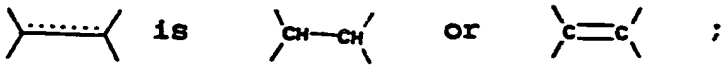
EP 0 259 621 A2

 or ,

and the other independently are H or C_{1-6}-alkyl,

wherein R' is H, C_{1-6}-alkyl, phenyl, thienyl, cyclopropyl, or C_{1-3}-alkoxymethyl; and

R^1 and R^6 independently are H or C_{1-6}-alkyl



and a salt thereof with a pharmaceutically-acceptable acid.

The new compounds are useful in improving the cognitive functions of the forebrain and hippocampus of mammals, and are useful in the treatment of Alzheimer's disease.

Piperidine Compounds and Their Preparation and Use.

The present invention relates to therapeutically active piperidine compounds, a method of preparing the same and to pharmaceutical compositions comprising the compounds. The novel compounds are useful as stimulants of the cognitive function of the forebrain and hippocampus of mammals and especially in the treatment of Alzheimer's disease.

Due to the in general improved health situation in the western world, elderly-related diseases are much more common now than in the past and are likely to be even more common in the future.

One of the elderly-related symptoms is a reduction of the cognitive functions. This symptom is especially pronounced in the patophysiological disease known as Alzheimer's disease. This disease is combined with, and also most likely caused by, a up to 90% degeneration of the muscarinic cholinergic neurons in nucleus basalis, which is part of substantia innominata. These neurons project to the prefrontal cortex and hippocampus and have a general stimulatory effect on the cognitive functions of the forebrain as well as of hippocampus , namely learning, association, consolidation, and recognition.

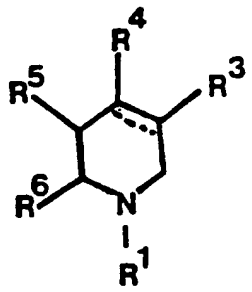
It is characteristic of Alzheimer's disease that although the cholinergic neurons degenerate, then the postsynaptic muscarinic receptors in the forebrain and hippocampus still exist. Therefore muscarinic cholinergic agonists are useful in the treatment of Alzheimer's disease and in improving the cognitive functions of elderly people.

It is well known that arecoline (methyl 1-methyl-1,2,5,6-tetrahydropiperidine-3-carboxylate) is such a cholinergic agonist.

Arecoline however has a very short biological half life and a small separation between central and pheripheral muscarinic effects. Furthermore arecoline is a rather toxic compound.

Accordingly it is an object of the invention to provide new muscarinic cholinergic compounds.

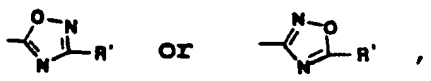
The novel compounds of the invention are piperidine compounds having the general formula I



I

wherein

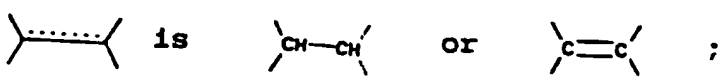
at least one of R^3, R^4 and R^5 are



and the other independently are H or C_{1-6}-alkyl,

wherein R' is H, C_{1-6}-alkyl, phenyl, thienyl, cyclopropyl, or C_{1-3}-alkoxymethyl ; and

R^1 and R^6 independently are H or C_{1-6}-alkyl

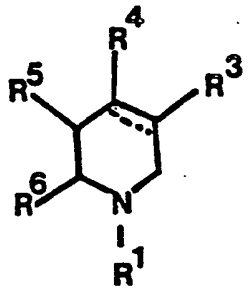


and a salt thereof with a pharmaceutically-acceptable acid.

Examples of such salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically-acceptable inorganic or organic acid addition salt.

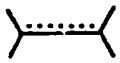
The invention also relates to a method of preparing the above mentioned compounds. This method comprises

a) reacting a reactive derivative of a compound having the general formula II



II

wherein R^1, R^6, and

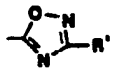


have the meanings defined above and

wherein one of R^3, R^4 and R^5 is CO_2H or a reactive derivative thereof, such as an ester, and the other independently are H or C 1-6-alkyl, with a compound having the formula III

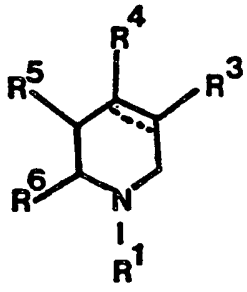
$$R'\text{-}C(C=NOH)NH_2 \qquad III$$

wherein R' has the meaning defined above to form a compound of the general formula I, wherein one of R^3, R^4 and R^5 is



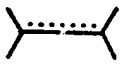
wherein R' has the meaning defined above,

b) reacting a compound having the general formula II



II

wherein R^1, R^6, and



have the meanings defined above and
wherein one of R^3, R^4, and R^5 is CN and the other independently are H or C_{1-6}-alkyl, with NH_2OH to form a compound having the general formula II wherein one of R^3, R^4, and R^5 is $C(=NOH)NH_2$ and the other independently are H or C_{1-6}-alkyl, and reacting this compound with R'-COCl or $(R'-CO)_2O$ to form a compound of formula I, wherein one of R^3, R^4, and R^5 is

wherein R' has the meaning defined above.

The pharmacological properties of the compounds of the invention can be illustrated by determining their capability to inhibit the specific binding of ^{3}H-QNB (^{3}H-quinuclidinyl benzilate) by 50%. The inhibitory effect of a substance on ^{3}H-QNB binding to brain membranes reflects the affinity of the substance for muscarinic acetylcholine receptors. (Yamamura, H.I. and Snyder, S.H., Proc.Natl.Acad.Sci. 71, 1725-29-(1979). The test is carryed out as follows:

Fresh whole forebrain from male Wistar rats (200-250 g) is homogenized by an Ultra-Turrax homogenizer (5-10 s) in volumes of 0.32 M sucrose. The homogenate is centrifuged at 4,300 × g for 5 min. The pellet is discarded and the supernatant centrifuged at 40,000 × g for 15 min. The final pellet is rehomogenized in 50 mM KH_2PO_4, pH 7.1 (1000 ml per g of original tissue) and this crude membrane preparation is used for binding assays. To 2.5 ml of tissue suspension is added 25µl of test solution * and 25µl ^{3}H-QNB (1 nM final concentration). Samples are thoroughly mixed and incubated at 37°C for 20 min. after incubation, samples are poured directly onto GF/C glass fiber filters under suction and immediately washed 2 times with 10 ml of buffer at 0°C. Non-specific binding is determined in dublicate using atropin (1µg/ml, final concentration) as the test substance. The amounts of radioactivity on the filters are determined by conventional liquid scintilation counting. Specific binding is total binding minus non-specific binding.

The test value will be given as IC_{50} (the concentration/µg/ml) of the test substance which inhibits the specific binding of ^{3}H-QNB by 50%.

IC_{50} = (applied test substance concentration)

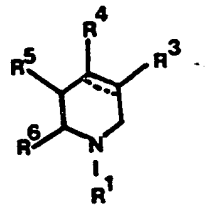
$$\times \frac{1}{\left(\frac{Co}{C_x} - 1\right)} \mu g/ml$$

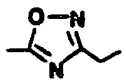
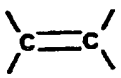
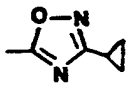
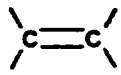
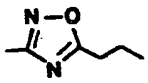
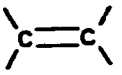
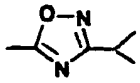
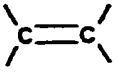
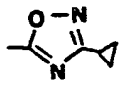
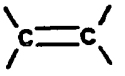
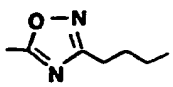
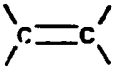
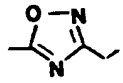
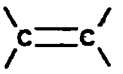
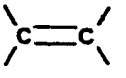
wherein C_o is specific binding in control assays and C_x is the specific binding in the test assay (the calculation assumes normal mass-action interaction).

Test results obtained by testing some compounds of the present invention will appear from the following table 1.

* Test compound is dissolved in 10 ml 96% ethanol (if necessary, acidified by 25µl 1N HCl and heated on a steambath for less than 5 minutes) at a concentration of 0.22 mg/ml. Three dilutions are made in 48% ethanol (1.1µg/ml, 11µg/ml and 110µg/ml). Concentrations of 10, 100 and 1000 ng/ml (final concentration) are added to duplicate assays. 25-75% inhibition of specific binding must be obtained, before calculation of IC_{50}.

TABLE 1



R^1	R^3	R^4	R^5	R^6	⟩⋯⋯⟨	Inhibition in vitro QNB binding (μg/ml)
CH_3		H	H	H		3.5
CH_3		H	H	H		2.0
CH_3		H	H	H		3.2
CH_3		H	H	H		4.9
H		H	H	H		4.7
CH_3		H	H	CH_3		3.3
H		H	CH_3	H		7.5
CH_3	CO_2CH_3	H	H	H		21.0

The compound of the invention, together with a conventional adjuvant, carrier, or diluent, and if desired in the form of a pharmaceutically-acceptable acid addition salt thereof, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective

muscarinic cholinergic agonistic amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing ten (10) milligrams of the active ingredient or, more broadly, one (1) to hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of this invention can thus be used for the formation of pharmaceutical preparations, e.g. for oral and parenteral administration to mammals including humans, in accordance with conventional methods of galenic pharmacy.

Conventional excipients are such pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral or enteral application which do not deleteriously react with the active compounds.

Examples of such carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Ampoules are conveniently unit dosages.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch, are particularly suitable for oral application. A syrup, elixir of the like can be used in cases where a sweetened vehicle can be employed.

Generally, the compounds of this invention are dispensed in unit form comprising 1-100 mg in a pharmaceutically acceptable carrier per unit dosage.

The dosage of the compounds according to this invention is 1-100 mg/day, preferably 10-70 mg/day, when administered to patients, e.g. humans, as a drug.

A typical tablet which may be prepared by conventional tabletting techniques contains:

Active compound 5.0 mg
Lactoseum 67.8 mg Ph.Eur.
Avicel™ 31.4 mg
Amberlite™IRP 88 1.0 mg
Magnesii stearas 0.25 mg Ph.Eur.

Due to the high muscarinic cholinergic receptor agonistic activity , the compounds of the invention are extremely useful in the treatment symptoms related to a reduction of the cognitive functions of the brain of mammals , when administered in an amount effective for stimulating the cognitive functions of the forebrain and hippocampus. The important stimulating activity of the compounds of the invention includes both activity against the patophysiological disease, Alzheimer's disease as well as against normal degeneration of brain function . The compounds of the invention may accordingly be administered to a subject, e.g., a living animal body, including a human, in need of stimulation of the cognitive functions of the forebrain and hippocampus, and if desired in the form of a pharmaceutically-acceptable acid addition salt thereof (such as the hydrobromide, hydrochloride, or sulfate, in any event prepared in the usual or conventional manner, e.g., evaporation to dryness of the free base in solution together with the acid), ordinarily concurrently, simultaneously, or together with a pharmaceutically-acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parenteral (including subcutaneous) route, in an effective forebrain and hippocampus stimulating amount, and in any event an amount which is effective for improving the cognitive function of mammals due to their muscarinic cholinergic receptor agonistic activity. Suitable dosage ranges are 1-100 milligrams daily, 10-100 milligrams daily, and especially 30-70 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

The invention will now be described in further detail with reference to the following examples:

EXAMPLE 1.

1-Methyl-3-(3-methoxymethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

To a solution of sodium ethoxide, (prepared from sodium (180mg;7,8 mmol)), destilled ethanol (20ml), molecular sieves (5g), and methoxymethylcarboxamide oxime (832 mg;8 mmol) were added. The mixture was stirred at room temperature for 10 min. whereafter arecoline, HBr (1,0g;4.23 mmol) was added. The mixture was heated at 80°C for 12 hours, filtered and evaporated in vacuo. To the residue was added water (10 ml) and the mixture was extracted with ether (3 × 25 ml). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. Upon disolving the residue in ethanol (99.9%)(5 ml) a solution of oxalic acid (350 mg;3,9 mmol) in ethanol (99,9%)(10 ml) was added. Addition of ether gave an analytically pure product in a yield of 500 mg (40%). M.P. 153-154°C.

EXAMPLE 2.

1-Methyl-3-(3-methyl-1,2,4-oxadiaxol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

This compound was synthesized as described above in example 1 using acetamide oxime instead of methoxymethylcarboxamide oxime. Crystallization gave the tittle compound in 44% yield. M.P. 159-160°C.

EXAMPLE 3.

(RS)-1-Methyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-piperidinium oxalate

The compound was synthesized as described above in example 2 using dihydroarecoline, HBr (Gloge et al., Br. J. Pharmac. Chemother. 27, 185, (1966)) instead of arecoline, HBr. Crystallization gave the title compound in 44% yield. M.P. 132-133°C.

EXAMPLE 4.

(RS)-1-Methyl-3-(3-ethyl-1,2,4-oxadiazol-5-yl)-piperidinium oxalate

The compound was synthesized as described above in example 3 using propionamide oxime instead of acetamide oxime. Crystallization gave the analytically pure title compound in 33% yield. M.P. 145-146°C.

EXAMPLE 5.

(RS)-1-Methyl-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-piperidinium oxalate

The compound was synthesized as described above in example 3 using cyclopropylcarboxamide oxime instead of acetamide oxime. Crystallization gave the title compound in 42% yield. M.P. 108-109°C.

EXAMPLE 6.

1-Methyl-4-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-piperidinium oxalate

The compound was synthesized as described above in example 5 using 1-methyl-4-ethoxycarbonyl-piperidinium chloride (Lambrecht and Mutschler, Arzneimittel Forsch.(Drug Res.) 23, 1427 (1973)) instead of dihydroarecoline. Chrystallization gave the title compound in 50% yield. M.P. 168-169°C.

EXAMPLE 7.

1-Methyl-4-(3-methyl-1,2,4-oxadiazol-5-yl)-piperidinium oxalate

The compound was synthesized as described above in example 6 using acetamide oxime instead of cyclopropylcarboxamide oxime. Crystallization gave the title compound in 53% yield. M.P. 173-174°C.

EXAMPLE 8.

1-Methyl-4-(3-propyl-1,2,4-oxadiazol-5-yl)-piperidinium oxalate

The compound was synthesized as described above in example 6 using butanamide oxime. Crystallazation gave the title compound in 33% yield. M.P. 117-118°C.

EXAMPLE 9.

1-Methyl-3-(3-propyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 1 using butanamide oxime instead of methoxymethylcarboxamide oxime. Crystallization gave the title compound in 32% yield. M.P. 153-154°C.

EXAMPLE 10.

1-Methyl-3-(3-ethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described in example 1 using propionamide oxime instead of methoxymethylcarboxamide oxime. Crystallization gave the title compound in 25% yield. M .P. 168-169°C.

EXAMPLE 11.

1-Methyl-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 1 using cyclopropyl carboxamide oxime instead of methoxymethylcarboxamide oxime. Crystallization gave the title compound in 34% yield. M.P. 169-172%°C.

EXAMPLE 12.

1-Methyl-3-(3-phenyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 1 using benzamide oxime instead of methoxymethylcarboxamide oxime. Crystallization gave the title compound in 16% yield. M.P. 185-186°C.

EXAMPLE 13.

a: 1-Methyl-1,2,5,6-tetrahydropyridin-3-carboxamide oxime

To a solution of sodium methoxide, prepared from sodium (575 mg; 25 mmol) in methanol (30 ml), hydroxylamononium chloride (1,74g; 25 mmol) was added. The mixture was stirred at room temperature for 30 min. and filtered. A solution of 1-methyl-3-cyano-1,2,5,6-tetrahydropyridine (Liberatore et al, Tetrahedron Letters 46, 4735, (1968)) (1,65 g; 13,5 mmol) in methanol (20 ml) was added to the filtrate. The reaction was stirred at room temperature for 20 hours and evaporated. The residue was extracted with ethanol (50 ml), filtrated and evaporated to give the title compound in 25% yield.

b: 1-Methyl-3-(5-methyl-1,2,4-oxadiazol-3-yl)-1,2,5,6-tetrahydropyridinium oxalate

A solution of 1-methyl-1,2,5,6-tetrahydropyridin-3-carboxamide oxime (200 mg; 1,29 mmol) in acetic anhydride (5 ml) was heated at 80°C for 24 hours. After evaporation in vacuo the residue was dissolved in 4N NaOH (5 ml) and extracted with ether (3 × 25 ml). The ether phases were dried ($MgSO_4$), filtered and evaporated in vacuo. The residue was dissolved in ethanol (99,9%) (5 ml) and added to a solution of oxalic acid (100 mg; 1,1 mmol) in ethanol (99,9%) (5 ml). Addition of ether gave the title compound in a yield of 52%. M.P. 173-174°C.

EXAMPLE 14.

1-Methyl-3-(5-ethyl-1,2,4-oxadiazol-3-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 13b using propionic anhydride instead of acetic anhydride. Crystallization gave the title compound in 38% yield. M.P. 181-182°C.

EXAMPLE 15.

1-Methyl-3-(5-propyl-1,2,4-oxadiazol-3-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described in example 13b using butyric anhydride instead of acetic anhydride. Crystallization gave the title compound in 65% yield. M.p. 170-171°C.

EXAMPLE 16.

a: 1-Methyl-4-carbamoyl-1,2,5,6-tetrahydropyridinium chloride

To a solution of ammonia in water (25%) (50 ml) was added 1-methyl-4-ethoxycarbonyl-1,2,5,6-tetrahydropyridinium chlorid (Lambrecht & Mutschler, Arzneimittel Forsch. (Drug Res.) 23, 1427 (1973)) (4,5 g; 21,9 mmol) and the mixture was stirred at room temperature for 20 hours. After evaporation in vacuo, the residue was recrystallized from methanol and ether. M.P. 191-192°C.

b: 1-Methyl-4-cyano-1,2,5,6-tetrahydropyridine

A solution of 1-methyl-4-carbamoyl-1,2,5,6-tetrahydropyridinium chlorid (3,6 g;20,4 mmol) in sodiumhydroxid (4N)(30ml) was extracted with methylenechlorid (3 × 50 ml). The combined extracts were dried, filtered and evaporated to 50 ml. To the extract a solution of triphenylphosphin (15,7 g; 60 mmol), bromine (3,3 ml; 65 mmol) and triethylamine (11 ml) in methylenechlorid (150 ml) was added. The reaction was stirred at room temperature for 20 hours and evaporated in vacuo. The residue was dissolved in water (50 ml) and washed with methylenechlorid (3 × 75 ml). To the water-phase sodiumhydroxid (4N) (30 ml) was added and the mixture was extracted with methylenechlorid. The combined extracts were dried, filtered and evaporated in vacuo to give the title compound.

c: 1-Methyl-1,2,5,6-tetrahydropyridin-4-carboxamide oxime

The compound was synthesized as described in example 13a using 1-methyl-4-cyano-1,2,5,6-tetrahydropyridine instead of 1-methyl-3-cyano-1,2,5,6-tetrahydropyridine.

d: 1-Methyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described in example 13b using 1-methyl-1,2,5,6-tetrahydropyridin-4-carboxamide oxime instead of 1-methyl-1,2,5,6-tetrahydropyridin-3-carboxamide oxime. Crystallization gave the title compound in 13% yield. M-P. 204-205°C.

EXAMPLE 17

1-Methyl-3-(3-isopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

816mg(8.0mmol) of isopropylcarboxamide oxime was added to a solution of sodium ethoxide (7.8 mmol) in 20 ml of destilled ethanol and 5g molecular sieves. The mixture was stirred at room temperature for 10 min whereafter 1.0g(4.23mmol) of arecoline,HBr was added. The mixture was heated at 80°C for 12 hours, filtered and evaporated in vacuo . 10ml of water was added to the residue and the mixture was extracted with ether (3 × 50 ml). The combined extracts were dried with $MgSO_4$ and evaporated in vacuo. The residue was dissolved in 5 ml of 99,9% ethanol and a solution of 380mg(4.23 mmol) of oxalic acid in 10 ml of 99,9% ethanol was added. Crystallization from ether gave the title compound in 37% yield. M.P. 133-134°C.

EXAMPLE 18

1-Methyl-3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 17 using pentanamide oxime instead of isopropylcarboxamide oxime. M.P. 121-123°C.

EXAMPLE 19

3-(3-Ethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described in example 17 using norarecoline, HCl and propionamide oxime instead of arecoline, HBr and isopropylcarboxamide oxime, respectively. M.P. 161-163°C.

The following compounds were synthesized in exactly the same way using butanamide oxime, pentanamide oxime, cyclopropylcarboxamide oxime and methoxymethylcarboxamide oxime, respectively.

3-(3-Propyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate. M.P. 162-163°C.

3-(3-Butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate. M.P. 207-208°C.

3-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate. M.P. 169-171°C.

3-(3-Methoxymethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate. M.P. 188-190°C.

EXAMPLE 20

a. 1-Ethyl-3-methoxycarbonyl-1,2,5,6-tetrahydro-pyridinium chloride

0.509ml (6.2mmol) of ethyliodide was added to a mixture of 1.0g(5.6mmol) norarecoline and 2.1g of potassium carbonate in 20 ml of acetone. The reaction mixture was refluxed for 16 hours, filtered and evaporated in vacuo. The residue was dissolved in 10ml aqueous of 4N sodium hydroxide and was then extracted with ether (3 × 50 ml). The combined ether phases were dried with ($MgSO_4$), filtered and evaporated in vacuo. The residue was dissolved in methanol and 10ml of 2.3 N hydrogen chloride in ether was added. Crystallization with ether gave the title compound.

b. 1-Ethyl-3-(3-ethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The title compound was synthesized as described in example 17 using 1-ethyl-3-methoxycarbonyl-1,2,5,6-tetrahydropyridinium chloride and propionamide oxime instead of arecoline, HBr and isopropylcarboxamide oxime, respectively. M.P. 150-151°C.

EXAMPLE 21

1-Ethyl-3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 20b using pentanamide oxime instead of propionamide oxime. M.P. 102-104°C.

EXAMPLE 22

a. 1-Propyl-3-methoxycarbonyl-1,2,5,6-tetrahydro-pyridinium chloride

The compound was synthesized as described in example 20a using propylbromide instead of ethyliodide. M.P. 173-174°C.

b. 1-Propyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described in example 17 using 1-propyl-3-methoxycarbonyl-1,2,5,6-tetrahydropyridinium chloride and acetamide oxime instead of arecoline, HBr and isopropylcarboxamide oxime, respectively. M.P. 64-66°C.

EXAMPLE 23

1-Propyl-3-(3-ethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 22 using propionamide oxime instead of acetamide oxime. M.P. 71-78°C.

EXAMPLE 24

a. (RS)-3-Methoxycarbonyl-5-methyl-1,2,5,6-tetrahydropyridinium oxalate

A solution of (RS)-3-carboxy-5-methyl-1,2,5,6-tetrahydropyridinium bromide (Krogsgaard-Larsen et al., Acta chem. Scand. B32, 327-334 (1978) in saturated methanolic hydrochloric acid was stirred for 17h at RT and evaporated in vacuo . The residue was dissolved in aqueous sodium hydroxide (4N) and extracted with ether. The combined organic phases were dried ($MgSO_4$), filtered and evaporated in vacuo. The residue was dissolved in ethanol and a solution of oxalic acid in ethanol was added. Crystallization from ether gave the title compound. M.P. 184-185°C.

b. (RS)-5-Methyl-3-(3-ethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described in example 17 using (RS)-3-methoxycarbonyl-5-methyl-1,2,5,6-tetrahydropyridinium oxalate and propionamide oxime instead of arecoline, HBr and isopropylcarboxamide oxime, respectively. M.P. 188-189°C.

EXAMPLE 25

(RS)-5-Methyl-3-(butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6--tetrahydropyridinium oxalate

The compound was synthesized as described in example 24b using pentanamide oxime instead of propionamide oxime. M.P. 189-191°C.

EXAMPLE 26

(RS)-1,6-Dimethyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described in example 17 using 1,6-dimethyl-3-ethoxycarbonyl-1,2,5,6-tetrahydropyridinium oxalate (Bishop, Z. Naturforsch. 25b, 1249-1251 (1970)) and acetamide oxime instead of arecoline, HBr and isopropylcarboxamide oxime, respectively. M.P. 115-117°C.

The following compounds were synthesized in exactly the same way using propionamide oxime and pentanamide oxime, respectively.

(RS)-1,6-Dimethyl-3-(3-ethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate. M.P. 148-149°C.

(RS)-1,6-Dimethyl-3-(3-butyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate. M.P. 141-142°C.

EXAMPLE 27

1-Methyl-3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-1,2,5,6-tetrahydropyridinium oxalate

0.182ml (2.0mmol) of cyclopropylcarboxylic acid chloride was added to a solution of 200mg (1.29 mmol) 1-methyl-1,2,5,6-tetrahydropyridin-3-carboxamide oxime in 8 ml DMF. The mixture was stirred at 55°C for 4 hours and evaporated in vacuo . The residue was refluxed with acetic acid for 16 hours. After evaporation in vacuo the residue was dissolved in 5ml 4N aqueous sodium hydroxide and was extracted with ether. The combined ether phases were dried with $MgSO_4$ and evaporated in vacuo. The residue contained both the title compound and 1-methyl-3-cyano-1,2,5,6-tetrahydropyridine. After chromatographic separations, the title compound crystallized with oxalic acid from ethanol and ether. M.P. 172-173°C.

EXAMPLE 28

1-Methyl-4-(5-ethyl-1,2,4-oxadaiazol-3-yl)-1,2,5,6-tetrahydropyridinium oxalate

A solution of 1-methyl-1,2,5,6-tetrahydropyridin-4-carboxamide oxime (200 mg; 1.0 mmol) in propionic anhydride (5 ml; 39 mmol) was stirred at 80°C for 20 hours. After evaporation in vacuo, the residue was dissolved in aqueous sodium hydroxide (4N) (5 ml) and extracted with ether (4 × 25 ml). The combined ether phases were dried ($Mg\ SO_4$), filtered and evaporated in vacuo. To a solution of the residue in ethanol (5 ml) a solution of oxalic acid (90 mg; 1.0 mmol) in ethanol (5 ml) was added. Crystallization with ether gave the title compound. M.P. 190-191°C.

EXAMPLE 29

1-Methyl-4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described in example 27 using 1-methyl-1,2,5,6-tetrahydropyridin-4-carboxamide oxime instead of 1-methyl-1,2,5,6-tetrahydropyridin-3-carboxamide oxime. M.P. 173-174°C.

EXAMPLE 30

(RS)-3-Methyl-5-(3-ethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described in example 17 using (RS,RS,RS)-4-hydroxy-5-methyl-3-methoxycarbonylpiperidinium chloride (Krogsgaard-Larsen et al., Acta Chem. Scand. B32, 327-334 (1978)) and propionamide oxime instead of arecoline, HBr and isopropylcarboxamide oxime, respectively. M.P. 186-187°C.

EXAMPLE 31

1-methyl-3-(3-(2-thienyl)-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 1 using 2-thiophen carboxamide oxime instead of methoxymethyl carboxamide oxime. Crystallization gave the title compound in 46% yield. M.P. 149-150°C.

EXAMPLE 32

1-methyl-3-(3-octyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 1 using nonanamide oxime instead of methoxymethyl carboxamide oxime. Crystallization gave the title compound in 19% yield. M.P. 122-123°C.

EXAMPLE 33

1-methyl-3-(3-pentyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinum oxalate

The compound was synthesized as described above in example 1 using hexanamide oxime instead of methoxymethyl carboxamide oxime. Crystallization gave the title compound in 40% yield. M.P. 149-150°C.

EXAMPLE 34

1-methyl-3-(3-heptyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 1 using octanamide oxime instead of methoxymethyl carboxamide oxime. Crystallization gave the title compound in 33% yield. M.P. 94-95°C.

EXAMPLE 35

3-(3-methyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 17 using norarecoline, HCl and acetamide oxime instead of arecoline, HBr and isopropyl carboxamide oxime, respectively. M.P. 172-173°C.

EXAMPLE 36

3-(3-isopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 17 using norarecoline, HCl instead of arecoline, HBr. M.P. 199-200°C.

EXAMPLE 37

3-(3-phenyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 17 using norarecoline, HCl and benzamide oxime instead of arecoline, HBr and isopropyl carboxamide oxime, respectively. M.P. 208-209°C.

EXAMPLE 38

3-(3-(2-thienyl)-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 17 using norarecoline, HCl and 2-thiophen carboxamide oxime instead of arecoline, HBr and isopropyl carboxamide oxime, respectively. M.P. 199-200°C.

EXAMPLE 39

1-methyl-4-(3-ethyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

Propionamide oxime (440 mg; 5,0 mmol), dicyclohexylcarbodiimide (1030 mg; 5,0 mmol) and 4-carboxy-1-methyl-1,2,5,6-tetrahydropyridinium chloride (886 mg; 5,0 mmol) were mixed in destilled DMF. The mixture was stirred at 60°C for 1 1/2 hour and evaporated in vacuo. To the residue was added water (50 ml) and the mixture was extracted with toluene (3×75 ml). pH was adjusted to 10 by means of 4N NaOH and extracted with toluene (3×100 ml). The combined extracts were dried (Na_2SO_4) and evaporated in vacuo. Upon dissolving the residue in ethanol (99.9%) (5 ml) a solution of oxalic acid (360 mg; 4,0 mmol) in ethanol (99.9%) (5 ml) was added. Crystallization gave the title compound in 15% yield. M.P. 170-171°C.

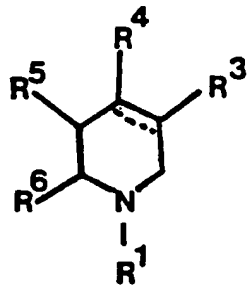
EXAMPLE 40

1-methyl-4-(3-phenyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridinium oxalate

The compound was synthesized as described above in example 39 using benzamide oxime instead of propionamide oxime. M.P. 172-173°C.

Claims

1. Piperidine compounds having the formula I



I

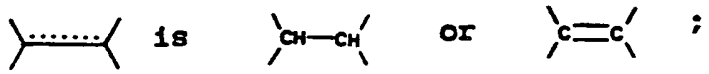
wherein

at least one of R^3, R^4, and R^5 are

and the other independently are H or C_{1-5}-alkyl,

wherein R' is H, C_{1-5}-alkyl, phenyl, thienyl, cyclopropyl, or C_{1-3}-alkoxymethyl; and

R^1 and R^6 independently are H or C_{1-5}-alkyl

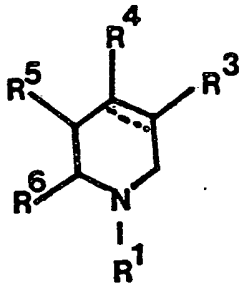


and a salt thereof with a pharmaceutically-acceptable acid.

2. A compound of claim 1 which is 1-methyl-3-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine

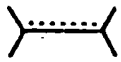
3. A method of preparing a compound according to claim 1, CHARACTERIZED in

a) reacting a reactive derivative of a compound having the general formula II



II

wherein R^1, R^6 and

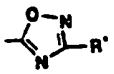


have the meanings defined above and

wherein one of R^3, R^4 and R^5 is CO_2H or a reactive derivative thereof, such as an ester, and the other independently are H or C_{1-5}-alkyl, with a compound having the formula III

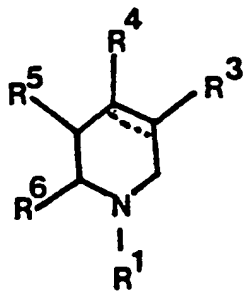
$$R'\text{-}C(=NOH)NH_2 \qquad III$$

wherein R' has the meaning defined above to form a compound of the general formula I, wherein one of R^3, R^4 and R^5 is



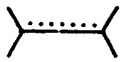
wherein R' has the meaning defined above,

b) reacting a compound having the general formula II



II

wherein R^1, R^6, and



have the meanings defined above and
wherein one of R^3, R^4, and R^5 is CN and the other independently are H or C_{1-6}-alkyl, with NH_2OH to form a compound having the general formula II wherein one of R^3, R^4, and R^5 is $C(=NOH)NH_2$ and the other independently are H or C_{1-6}-alkyl, and reacting this compound with R'-COCl or $(R'-CO)_2O$ to form a compound of formula I, wherein one of R^3, R^4, and R^5 is

wherein R' has the meaning defined above.

4. A pharmaceutical composition suitable for use in stimulating the cognitive functions of the forebrain and hippocampus of mammals, including humans, and in treating Alzheimer's disease, comprising an amount of a compound of claim 1 or 2 which is effective for the stimulation of the forebrain and hippocampus of mammals or treating Alzheimer's disease together with a pharmaceutically-acceptable carrier or diluent.

5. A pharmaceutical composition according to claim 4 wherein it is in the form of an oral dosage unit containing 1-100mg of the active compound.